potentially useful in treating various trapped gas syndromes that do not respond to conventional methods.

KENNETH W. KIZER, MD, MPH
Consultant in Diving and Hyperbaric Medicine
University of California, San Francisco Medical Center
San Francisco
President-Elect
North Pacific Chapter, Undersea Medical Society, Inc.

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Alkalinization Therapy for Tricyclic Antidepressant Overdose

TO THE EDITOR: I appreciated the insight into treatment of cardiac arrhythmias caused by tricyclic antidepressant overdose provided by Hoffman and McElroy in their recent article.[1] However, I take issue with the recommendation that "alkalinization therapy" be used to treat quinidine overdose. One of the authors' own references[2] actually states that quinidine urinary excretion is inversely related to urine pH, and that QT lengthening, a quinidine-induced effect, increases as urine pH increases. This suggests that urine pH exerts a clinically significant effect.

Two other references cited by Hoffman and McElroy[3,4] mention administration of alkalinizing drugs during quinidine toxicity, but only in combating the patients' preexisting metabolic acidosis. In neither case was *alkalinization* considered the major thrust of treatment, and both articles mention that although this procedure has been advocated, it has not always proved beneficial.

A case which illustrates the potential danger of an alkaline urine pH concomitant with quinidine administration was reported by Zinn in 1970.[5] In a patient whose condition was stabilized with constant doses of quinidine and digoxin, electrocardiographic signs of quinidine toxicity began to occur. A quinidine level subsequently obtained was 25 μg per ml. When questioned, the patient was found to have begun recently making his urine alkaline with his diet and antacid tablets. Upon return to a normal diet, quinidine serum levels returned to the therapeutic range at his previous dose.

The administration of sodium bicarbonate may be necessary in treating quinidine toxicity if metabolic acidosis has occurred. In this case it would be used in conjunction with specific measures to combat quinidine's ill effects (hypotension, convulsions, arrhythmia). Sodium bicarbonate should not be advocated as one of these specific measures.

MARY LINDA H. STOTTER, PharmD
Methodist Hospital of Indiana
Indianapolis

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TO THE EDITOR: I read with interest Hoffman and McElroy's excellent article on bicarbonate therapy in tricyclic antidepressant overdose in the January 1981 issue.[1] I was glad that they have thereby focused attention on this somewhat neglected and quite effective treatment. It thus pains me to nitpick an excellent presentation, but their discussion of phenytoin deserves some amplification.

First, an error apparently occurred in preparation of the manuscript, and the reference cited[2] regarding the ineffectiveness of phenytoin (diphenylhydantoin) contains no mention of that drug whatsoever. There is, in fact, scant literature on this topic. Until recently, there was only one published report recommending phenytoin in humans, and this did not mention the number of cases or the results. The authors suggested a dose of either 200 mg given intramuscularly or 5 to 10 mg per kg of body weight intravenously as a useful prophylactic agent against "cardiac or cerebral arrhythmias."[3] Also until recently, the only other published data involved three dogs given amitryptyline until arrhythmias developed. Intravenously given phenytoin in varying doses had a brief antiarrhythmic effect at that time, but sinus rhythm was not restored.[4] At the same time, pulse and blood pressure fell significantly and respirations were depressed, even in the one animal receiving only 2 mg per kg of body weight. The two animals that received 15 to 17 mg of phenytoin per kg of body weight died several hours later.

Fortunately, the most detailed report yet made

has just been published.[5] This study of ten humans, all with QRS prolongation of 100 to 160 msec, clearly documented a mean decrease in QRS prolongation of 24 msec over a mean time of 39 minutes after intravenous loading with 5 to 7 mg phenytoin per kg of body weight. Other drugs were withheld, and acid balance and fluid volume were maintained at normal values. Although potential effects on preexisting hypotension were not evaluated, the conduction abnormalities were clearly reversed, and no further arrhythmias occurred in any of these patients. Thus, phenytoin seems a useful drug that warrants further investigation, although bicarbonate therapy or hyperventilation to a pH of 7.5 remains the most benign and thoroughly evaluated treatment.

MICHAEL CALLAHAM, MD
Associate Chief, Emergency Medicine
Highland General Hospital
Oakland, California

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Drs. Hoffman and McElroy Respond

TO THE EDITOR: We were pleased to review these two thoughtful letters regarding topics covered somewhat peripherally in our paper on alkalinization therapy for tricyclic antidepressant overdose. While neither addresses the major thrust of our article, both raise issues that are of significant interest.

Dr. Stotter is concerned about the use of alkalinization in patients with quinidine overdose. She correctly makes the point that this drug's urinary excretion is inversely related to urine pH,[1] which would tend to suggest that the use of sodium bicarbonate might in fact be harmful in such patients. We feel that there may be, nevertheless, overriding arguments in favor of bicarbonate in this situation. Serum quinidine levels are poor indicators of level of toxicity,[2] as the large majority of the drug is bound to protein and lipid moieties of the cell membrane.[3] It is thus not clear that the rate of excretion is a critical factor in this drug's toxicity. Furthermore, increasing serum pH increases protein binding of quinidine,[4] so that free drug levels do in fact decrease with alkalinization. Perhaps most important, hypokalemic effects of alkalinization may be critical in controlling the cardiotoxic effect of quinidine overdosage.[2,5] Unfortunately, empirical data on this subject are minimal. Nevertheless, there is reason to believe it may have significantly positive effects, and we believe it deserves further study.

We were somewhat surprised to read Dr. Callaham's objection to our brief discussion of the use of phenytoin in tricyclic antidepressant overdose. Let us first note that Dr. Callaham was in fact correct in assuming that there was a manuscript error with regard to our referencing. The appropriate reference was to number 33, an article by Bismuth and co-workers,[6] rather than 32, as mistakenly given. The Bismuth article, and several others,[7-10] referred to in Dr. Callaham's own excellent review of this subject, suggests a very limited role for phenytoin. Dr. Callaham concluded his own discussion of phenytoin (published in October 1979) as follows: "No well-described case documenting its effectiveness has been published, and it is illogical to advocate its use under these circumstances."

The recent article by Hagerman and Hanashiro,[12] to which Dr. Callaham refers in his letter, is indeed intriguing. The uniformly successful response to phenytoin in ten patients with prolonged QRS complexes or PR intervals (or both) should encourage further investigation. However, no blood levels were reported, none of the patients were acidotic, nor was there any other suggestion in the report that any of them was hypotensive. Likewise, the only dysrhythmia apparently seen in any of these patients was sinus tachycardia.

The role of phenytoin in the treatment of severe tricyclic antidepressant overdose remains unclear. Our own anecdotal experience has not been encouraging, and we see no reason, at this time, to alter our suggestion that alkalinization, combined with appropriate fluid management, is the treatment of first choice for hypotension and dysrhythmia secondary to tricyclic antidepressant overdose.

JEROME R. HOFFMAN, MD
Assistant Professor of Medicine
UCLA Emergency Medicine Center
CHARLES R. McELROY, MD
Associate Professor of Medicine
Director, UCLA Emergency Medicine Center
Los Angeles

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